specification by these changes. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. §112, first paragraph, for lack of enablement**. Claims 35-51 stand rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Examiner states that "applicants have not enabled one to obtain the requisite isomer with a purity of 96% or greater." Applicant disagrees.

Applicant respectfully submits that the procedure disclosed on page 21, lines 12-28, teaches a procedure by which one of skill in the art can separate the L-Pro-D-boroPro from the L-Pro-L-boroPro isomer and thereby obtain the claimed invention.

> "High pressure liquid chromatography (HPLC) can be used to separate L-Pro-D-boroPro from L-Pro-L-boroPro. A 4.6 mm x 250 mm Nucleosil C18 (5μ particle) column employing a two buffer system (Buffer A is 100% H2O with 0.1% TFA, and buffer B is 70% CH3CN, 30% H2O, 0.86% TFA) can be used to carry out the separation. From 0 to 5 min 5% B and 95% A is used, and from 5 to 25 min 5% to 100% B is used. The L,L isomer comes off first at about 7 min, followed by the L,D isomer at about 10 min. NMR and mass spectra analysis were consistent with both compounds being Pro-boroPro. Rechromatography of the purified isomers indicated that the first pass on the HPLC column achieved an isomeric purity of about 99-6% for each isomer. High pressure liquid chromatography (HPLC) can similarly be used to be used to separate L-Ala-D-boroPro from L-Ala-L-boroPro or to separate the D-boroPro form of other inhibitors from the L-boroPro form."

As stated in the originally filed Specification, the disclosed procedure allows one to obtain "an isomeric purity of about 99-6%" with just one pass over the HPLC column. Therefore, the present application would allow one of ordinary skill in the art to practice and use the claimed invention. Applicant requests that the rejection be removed.

The Examiner points out that there are four different isomers of Ala-boroPro, *i.e. cis*-L-Ala-D-boroPro, *cis*-L-Ala-L-boroPro, *trans*-L-Ala-D-boroPro, and *trans*-L-Ala-L-boroPro. The

the two isomers. Since the boroproline residue of the peptides is constantly interconverting between the *trans* state and the *cis* state, the procedure disclosed on page 21 of the Specification would result in a mixture of *cis* and *trans* isomers. However, this point is not pertinent to the claims since the Applicant is not claiming a specific *cis* or *trans* isomer. The Applicant is only required to teach one of ordinary skill in the art how to separate the optical isomers, *i.e.*, L-boroPro versus D-boroPro, because that is what is claimed.

Examiner has also said that "one would have to 'know' that (a) the procedure on page 15, lines 3+ must be ignored, and (b) the procedure on page 21 is incomplete". Examiner is therefore leveling a rejection that the claims are not enabled because the Specification includes a teaching that does not work. This is not the standard. The Specification is enabling if it teaches what <u>does</u> work. As discussed above, the Specification teaches the effective separation at page 21, lines 12-28.

It is true that, in some instances the Specification can be found non-enabling if, when taken as a whole, the teachings of the Specification would not achieve the claimed invention. That, however, is certainly not the case here. In regard to the procedure, on page 15, lines 3-11, which does not achieve the claimed invention, one of skill in the art would appreciate that the Applicant is only making a hypothesis that the early fraction is enriched in one isomer. As evidence to this, the Applicant uses the word "appears" as an indication that the results are only speculative. Those of ordinary skill in this art would understand this to be a suggestion and not a definitive conclusion. On the other hand, a demonstration that HPLC works clearly would be seen by one of ordinary skill as an appropriate and effective means of separating the stereoisomers. Clearly, one of ordinary skill in the art reading the Specification would understand and appreciate that the HPLC-based purification method would yield a separation of the boroproline stereoisomers; therefore, the Specification is enabling for the claimed invention.

II. <u>Rejection under 35 U.S.C. §112, first paragraph, for lack of written description</u>.

Claims 35-51 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application [illegible]

specification for stereochemical purities of 96%, 97%, 98%, and 99% with respect to the carbon atom bearing boron. Applicant respectfully disagrees. Applicant also submits that claims reciting these limitations were added to the application in an Amendment filed September 4, 1998, which was filed in response to the first Office Action in this case. Since the filing of these claims reciting a stereochemical purity of 96%, 97%, 98%, and 99%, there have been no less than four subsequent Office Actions in this case. Only in the last Office Action was a rejection of these limitations issued. Applicant respectfully points out that under 37 C.F.R. §1.104(a)-(b) the Applicant is entitled to a timely and thorough review of the application including amendments submitted and is also entitled to an Examiner's action "complete as to all matters."

One of ordinary skill in the art reading the specification would understand that clearly the Applicant had these percentages in mind at the time of filing. As evidence, the Applicant on page 21 at line 24 of the specification recites "an isomeric purity of about 99-6% for each isomer." One of ordinary skill in the art reading this phrase would understand it to mean an isomeric purity of about 99-96% for each isomer. It is a common practice to drop the first digit or digits if it is the same as in the first number recited. For example, in the citations of scientific papers it is common to recite the page numbers in this manner—"10023-30" to mean "10023-10030". Therefore, the Applicant submits that there is adequate support in the specification for percentages between 99% and 96% and requests that the rejection be removed.

Also, isolating a more optically pure mixture would clearly be a goal of any chemists looking to purify a mixture of optically active compounds. Therefore, other percentages in the range of 95% to 100% would be understood by one of ordinary skill in the art. Applicant submits that the claimed invention was adequately described explicitly as described above and implicitly in the as-filed specification and requests that the rejection be removed.

To provide even further support for the Applicant's position that the claims do not lack written description support, Applicant respectfully directs the Examiner to the case of In re Johnson (558 F.2d 1008, 194 USPQ 187 (CCPA 1977)), in which this issue was addressed. Johnson sought to limit his claims drawn to a genus of polymers by excluding two species, which had been the subject of a lost count in an interference. The Patent Office held that Johnson was not entitled to the original filing date of July 16, 1963 b[illegible]

paragraph of 35 U.S.C. §112." The Board of Appeals affirmed the Examiner's rejection. However, the CCPA in this case reversed the rejection under 35 U.S.C. §112 and held:

> "The notion that one who fully discloses and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute."

A copy of this decision has been provided for the convenience of the Examiner. In light of the court's opinion, the limitations of 96%, 97%, 98%, and 99% are adequately described in the as filed specification, and therefore, the applicant requests that the rejection under 35 U.S.C. §112, first paragraph, for lack of written description be removed.

III. **Rejection under 35 U.S.C. §112, second paragraph, as being indefinite**. Claims 35-51 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. As suggested by the Examiner, the Applicant has amended claims 35 and 42 to recite "A mixture consisting of a compound of the following structure and at least one stereoisomer thereof". Applicant has also amended claims 35 and 42 to include a hyphen between "DP" and "IV" as suggested by the Examiner.

Examiner also states that the phrase "capable of being hydrolyzed" in claims 35 and 42 is "indefinite as to whether the hydrolysis occurs at all." Applicant submits that the phrase "capable of being hydrolyzed" is definite, and in support of this conclusion Applicant has included with this Response a copy of U.S. Patent 4,935,493, which uses the same language as the instant claims (see claims 1 and 11 of the '492 patent). Applicant submits that the phrase "a group capable of being hydrolyzed to a hydroxyl group at physiological pH" would be definite to one of skill in this art. For consistency between the earlier '492 patent and the present application, Applicant wishes to avoid amending the claims especially since the language "a group capable of being hydrolyzed" and "a group which is hydrolyzed" would appear to have the same effect in the claims.

IV. **Rejection under 35 U.S.C. §103, as being unpatentable over the prior art**. Claims 35-51 have been rejected under 35 U.S.C. §103, as being unpatentable over Bachovchin (*J. Biol. Chem.* 265:3738-3743, 1990) or Bachovchin *et al.* (U.S. Patent 4,935,493) or Bachovchin *et al.* (WO 89/03223) or Flentke (*Proc. Natl. Acad. Sci. USA* 88:1556, 1991). Examiner has argued that it would have been obvious to one of ordinary skill in the art to use a C_{18} column rather than the silica gel column used in Bachovchin *JBC* 1990 to separate the stereoisomers of boroproline derivatives. Applicant respectfully disagrees.

Applicant submits that the Examiner does not establish a proper *prima facie* case of obviousness because the Examiner (1) points to no teaching or motivation to obtain compositions that are ≥96% enriched for one stereoisomer; (2) points to no teaching or suggestion of how a separation of the stereoisomers could be accomplished even if such a composition were desired; and (3) fails to establish that, even if it were obvious to try to obtain such a composition, it could be accomplished with a reasonable expectation of success.

First in order for one of skill in the art to be motivated to prepare a composition that is ≥96% enriched in one stereoisomer, he must have some reason to want to separate the isomers. Moreover, in order to be motivated to prepare a composition enriched for the *L*-isomer in particular, the person would need to have some reason for selecting that isomer. The prior art provides no teaching or suggestion that one isomer is more desirable than the other, and certainly provides no suggestion that the L-isomer is more effective than the D-isomer. By contrast, the present invention teaches that the L-isomer is more active than the D-isomer. The invention therefore teaches that it is desirable to separate the isomers, and that it is desirable to prepare compositions enriched in the L-isomer.

Even if the prior art did provide a motivation to try to separate the isomers, no teaching or suggestion of a method for achieving such a result is provided. Examiner takes the position that it would have been obvious for one of skill in the art to try a C_{18} column. Examiner even offers numerous motivations for using a C_{18} column including (1) "C_{18} is the single most commonly used HPLC column in existence," (2) "a chemist might choose to use this because of his own (positive) experience with it," (3) "his lab only has C_{18} HPLC columns and no silica HPLC columns," (4) "perhaps the C_{18} columns are less expensive that (sic) the silica HPLC [illegible]"

general. None are specific to the claimed invention. From the teachings in the art, it is not even obvious that HPLC rather than TLC or recrystallization techniques could be used to achieve the claimed invention. Therefore, Applicant respectfully disagrees that it would have been obvious to use a C_{18} column.

Given the multitude of columns (*e.g.*, silica gel, C_1, C_4, C_8, C_{18}, C_{30}, phenyl, *etc.*), sizes of columns (*e.g.*, length and diameter), brands of columns, separation techniques (*e.g.*, gel permeation, ion exchange, size exclusion, normal phase, hydrophobic interaction, *etc.*), and particle sizes of packing material in columns that are available in the art, it was not at all obvious which column would yield a separation of the stereoisomers. If need be, Applicant is willing to provide evidence showing that all these columns and matrices were available at the time the invention was made. The method of purifying the stereoisomer is further complicated when one considers the solvents or mixtures thereof needed in separating the isomers using a particular column. Given the vast array of columns and solvents available at the time the invention was made and all the permutations thereof, it is all but obvious which set of parameters would lead to a successful purification method. The art provides no teaching or suggestion that would lead one of ordinary skill in the art to select a C_{18} column from all of these choices.

Furthermore, even if it were obvious to try to separate the isomers, to try to prepare a composition enriched in the L-isomer, and to try to use a C_{18} column to do so, there is no teaching of a reasonable expectation of success in using a C_{18} column to separate the stereoisomers of boroproline derivatives. Given the myriad of columns and purification schemes, it would not be obvious from the prior art which would be successful and which not. Without such a teaching the combined references cannot render the claimed invention obvious.

In regard to the Examiner's statement: "if applicants believe that they are the first to discover the existence of C_{18} columns, and would like to see references (published prior to April 14, 1990) discussing C_{18} column chromatography, such references will be provided", Applicant humbly submits that they did not discover C_{18} columns but they *did* discover the use of C_{18} columns in the purification of stereoisomers of the claimed boroproline derivatives.

The Applicant respectfully submits that given the lack of motivation to purify the stereoisomers, the lack of teaching how to effect the purification and the lack of

expectation of success the combined references do not render the claimed invention obvious. Therefore, Applicant requests that the rejection be removed.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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